

REMARKS

Claims 1, 3-12, 15, 16, 18-26 and 69 remain before the Examiner for reconsideration. Claims 13-14, 17, 27-68, and 70-103 have been withdrawn. Claim 2 has been canceled without prejudice.

In the Office Action dated July 2, 2008 the Examiner rejected Claim 12 under 35 U.S.C. 112, second paragraph, "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention", asserting:

Specifically claim 12 does not further limit claims 1 or 7 since claim 1 already recites that the multifunctional isocyanate is derived from an aliphatic compound, thus the claim is indefinite with respect as to how the claim is further limiting claims 1 and 7. This new rejection was necessitated by applicant's amendments to the claims.

Applicants have amended claim 12 to obviate the Examiner's rejection.

The Examiner further indicated that Applicant's arguments made in the Amendment filed April 30, 2008, "with respect to the 102(b) rejection over Chen have been fully considered and are persuasive," and the Examiner withdrew the rejection over Chen. Applicants gratefully acknowledge the Examiner withdrawal of the rejection over Chen.

However, the Examiner rejected claims 1,3,7-8,10-12,19-22,27,34-35 and 69 under 35U.S.C. 102(b) "as being anticipated by Lipatova et al. (Macromol. Symp. 152,139-150 (2000)), for the reasons set forth in the previous office action filed 11/30/2007". Specifically, the Examiner asserted that:

Applicant's arguments filed 04/30/2008 have been fully considered but they are not persuasive.

Applicants assert that Liptova discloses specifically only toluene diisocyanate (TDI) and does not teach the use of a multifunction isocyanate derived from an aliphatic compound. Applicants further assert that there is no disclosure within Liptova of release of heparin or any other bioactive agent within a living organism and applicants further assert that heparin is not likely to be released upon degradation of the polyurethane.

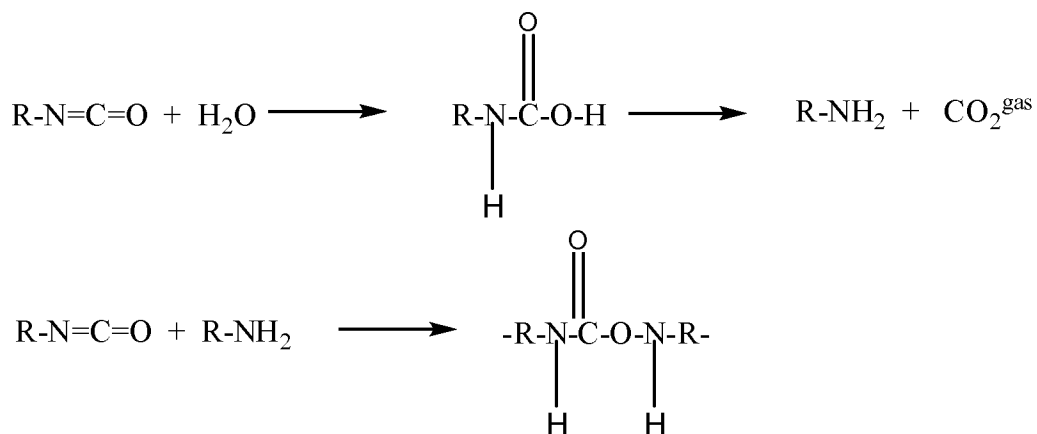
The examiner respectfully disagrees with the above assertions by applicants. Firstly Liptova clearly teaches the use of aliphatic diisocyanates such as hexamethylene diisocyanate (HDI). Regarding applicant's assertion that it would be impossible to determine if heparin would be a degradation product and if it would be released into the

body, since Lipatova anticipates applicants claimed composition the examiner assumes that it must be capable of biodegrading and releasing the bioactive within a living organism. Besides the recitation that the polyurethane composition releases a bioactive agent within the body by degradation is an intended use type of limitation for the composition. A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim.

Applicants respectfully traverse the Examiner's rejection.

Applicants respectfully assert that it is not clear that Liptova teaches the use of an aliphatic diisocyanates such as hexamethylene diisocyanate in connection with heparin. Data is provided in Figure 4 only for polyurethanes composed of 1,3,6-diphenylmethanediisocyanate (DPM), poly(tetramethylene), dihydrazide of adipic acid and heparin. Polyurethanes "based on "hexamethylene diisocyanate, poly(tetramethylene glycol) M=1---, and ethylene glycol" are discussed on page 148, but it is not clear is such polyurethanes also included heparin.

In any event, there is absolutely no disclosure in Liptova of reacting isocyanate groups of at least one multifunctional isocyanate compound with at least one bioactive agent having at least one reactive group -X which is a hydroxyl group (-OH) or an amine group (-NH₂) in a solution with water. In connection with other references, such as Beckman et al. discussed below, the Examiner has asserted incorrectly that the fact that the isocyanates of the present invention are reacted with the at least one bioactive agent in solution with water is "of little concern since applicants attempted limitation that the isocyanate compound and bioactive agent are reacted in a solution with water is a product by process type of limitation." The Examiner is correct that the claims of the present invention are drawn to a polyurethane composition. However, as clear to one skilled in the art, the process used to make the polyurethanes of the present invention, in which water is present, clearly leads to a patentable distinction from the prior art. In that regard, as clear to one skilled in the art of isocyanate and polyurethane chemistry, isocyanates are highly reactive with water, and the presence of water in the reaction mixture has substantial effects upon the chemical composition and physiochemical properties of the resultant composition as, for example, represented in the following exemplary reaction scheme (wherein R is the residue of the isocyanate):



Indeed, water acts as a chain extender. The water reaction in the present invention yields a di-substituted urea -R-NH-CO-NH-R- and gaseous carbon dioxide (CO_2). The water reaction substantially affects the morphology of the polyurethane through the release of the carbon dioxide (CO_2) gas, which results in foaming and a porous morphology.

Lipatova et al., which does not disclose or suggest reacting isocyanate groups of at least one multifunctional isocyanate compound with at least one bioactive agent in a solution with water, clearly does not and cannot anticipate the presently claimed invention.

The Examiner also rejected Claims 1,3-12,15-16,19-20,22,25 and 69 under 35 U.S.C. 102(e) "as being anticipated by Beckman et al. (US 7,264,823 B2), for the reasons set forth in the previous office action filed 11/30/2007. Specifically, the Examiner asserted that:

Applicant's arguments filed 04/30/2008 have been fully considered but they are not persuasive.

Applicants assert that the adhesives of Beckman are formed in the absence of water as shown by the examples, which is in contrast to applicant's claimed invention which requires that the multifunctional isocyanate compound are reacted with at least one bioactive agent in solution with water.

The relevance of these assertions is unclear. Firstly as mentioned by applicants response Beckman's adhesives have isocyanate groups that reacts with tissues and moisture in the surrounding tissue, thus it would appear that the adhesive is reacted with water. Secondly the examples within Beckman were given solely for the purpose of illustration and were not to be construed as being limiting to their invention since many variations are possible without departing from the spirit and scope of the invention. However the facts above are of little concern since applicants attempted limitation that the isocyanate compound and bioactive agent are reacted in a solution with water is a product by process type of limitation. Applicants claims are drawn to a

polyurethane composition, thus the process to make the polyurethane does not lead to a patentable distinction from the prior art, therefore since the product produced in Beckman is the same as applicants claimed invention the limitations are considered met. "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985).

Applicants respectfully traverse the Examiner's rejection.

Once again, Beckman et al. discloses an adhesive which includes isocyanate functionality that reacts with tissue and/or moisture surrounding tissue to adhere tissue. The adhesives of Beckman et al. must be formed in the absence of water. See, for example, Examples 1 through 10. In that regard, the presence of water in the reactions of Beckman et al. would cause reaction of all isocyanate functionality in the compounds of Beckman et al., and thereby render the compounds of Beckman et al. ineffective as adhesives.

To the contrary, in the present invention, multifunction isocyanate compound are reacted with at least one bioactive agent in a solution with water. Unlike the compositions of Beckman et al., the polyurethane compositions of the present invention do not contain reactive isocyanate groups.

Contrary to the present invention, compounds having isocyanate reactive functionalities such as polysaccharides, peptides, proteins, steroids etc. of Beckman et al. are reacted with the multisocyanate compounds of Beckman et al. in the absence of water. Only after, such compounds of Beckman et al. are reacted with an excess of multiisocyanate functionality to create the isocyanate functional adhesives of Beckman et al. are such adhesives exposed to a very limited amount of moisture/water at a wound site. To the contrary, the bioactive compounds of the present invention are reacted with the multiisocyanate compounds of the present invention in the presence of water. Thus, in the present invention, the bioactive compounds and water react simultaneously with the multiisocyanate compound, destroying all isocyanate functionality, and resulting in compounds of very different composition and morphology than the adhesives of Beckman et al.

The Examiner rejected claims 1,3-4,7-8,12,19,22,27-30,33 and 69 under 35 U.S.C.

102(e) “as being anticipated by Woodhouse et al. (US 6,221,997 B1), for the reasons set forth in the previous office action filed 1113012007”. Specifically, the Examiner asserted that:

Applicant's arguments filed 04/30/2008 have been fully considered but they are not persuasive.

Applicants assert that Woodhouse's polyurethanes are formed in the absence of water, which is in contrast to applicant's claimed invention which requires that the multifunctional isocyanate compound is reacted with at least one bioactive agent in solution with water. Applicants further assert that water is considered as a contaminant that would negatively impact the mechanical properties of the polyurethanes of Woodhouse.

The relevance of these assertions is unclear. As stated above in the response for Beckman applicant's attempted limitation that the isocyanate compound and bioactive agent are reacted in a solution with water is a product by process type of limitation. Applicants claims are drawn to a polyurethane composition, thus the process to make the polyurethane does not lead to a patentable distinction from the prior art, therefore since the product produced in Woodhouse is the same as applicants claimed invention the limitations are considered met.

Applicants respectfully traverse the Examiner's rejection.

As described above, the Examiner cannot ignore the claim limitation that the least one multifunctional isocyanate compound of the present invention is reacted with the at least one bioactive agent of the present invention in a solution with water. See, for example, Ex Parte Murphy and Burford, 217 USPQ 479, 481 (P.O. Bd. Appls. 1982) (“it is error to ignore specific limitations distinguishing over the cited reference”); In re Boe, 505 F.2d 1297, 184 USPQ 38 (CCPA). Once again, the presence of water in the formation of the polyurethanes of the present invention results in substantial changes in chemical composition and physiochemical characteristics as compared to the case in which a polyurethane is formed in the absence of water, as in the case of Woodhouse et al. As clear to one of ordinary skill in the art, and contrary to the Examiner's assertion, the product produced in Woodhouse (in which di-substituted ureas resulting from reaction with water as described above are absent) is not the same as the presently claimed polyurethanes.

The Examiner further rejected claims 1,3-12,15-16,18-26 and 69 under 35 U.S.C. 103(a) “as being unpatentable over Zhang et al. (Biomaterials 21 (2000) 1247-1258) in view of Liptova et al. (Macromol. Symp. 152, 139-150 (2000)) or in view of Woodhouse et al. (US

6,221,997 B1), for the reasons set forth in the previous office action filed 1113012007". Specifically, the Examiner asserted that:

Applicant's arguments filed 04/30/2008 have been fully considered but they are not persuasive.

Applicants assert there is no disclosure or suggestion within Zhang of the reaction of a protein or any other bioactive agent with a multifunctional isocyanate compound and Zhang does not even mention what is meant by incorporation of proteins.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Clearly the examiner noted that Zhang while disclosing the peptide based urethane polymer may allow incorporation of proteins of interest such as cell attachment and/or growth factors but does not give any working examples, which is why the reference was combined with the other two other references in a 103(a) obviousness type of rejection. From the disclosures of Liptova and Woodhouse it would have been obvious to one of ordinary skill in the art that polyurethanes of Zhang could be conjugated to bioactive substances such as peptides and heparin.

Applicants respectfully traverse the Examiner's rejection.

The Examiner had earlier admitted that Zhang et al. is not enabling for covalent attachment of proteins within the polyurethane thereof. Once again, Zhang does not disclose even what is meant by incorporation of proteins. In that regard, in the present invention an isocyanate group of at least one multifunctional isocyanate compound is reacted with the bioactive agent in solution with water, thereby covalently bonding the bioactive agent within the polyurethane composition. There is no disclosure or suggestion in Zhang et al. of the reaction of a protein or any other bioactive agent in solution with water with a multiisocyanate compound to form a polyurethane which is biodegradable to release the bioactive agent within a living organism.

Although the Examiner is correct that one cannot show nonobviousness by simply attacking references individually where the rejections are based on combinations of references, this means only that a reference cannot be read in isolation and must be read for what it fairly teaches one skilled in the art in combination with the prior art as a whole. *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). It is well established that, in determining obviousness, one must determine the scope and content of the prior art and ascertain the differences between the

prior art and the claims at issue. *Graham v. John Deere* 383 U.S. 1, 17-18, 86 S. Ct. 684, 15 L. Ed. 2d 545, (1966). The Examiner cannot ignore the Graham requirement of establishing that all the elements of the claimed invention are set forth in the prior art by simply asserting that the Applicants cannot attack references individually.

For the reasons set forth above, one cannot combine the disclosure of Zhang et al. with the disclosure of Lipatova et al., Woodhouse et al. or any combination thereof to arrive at the present invention. Once again, neither Lipatova et al. nor Woodhouse et al. disclosure or suggest reaction of the least one multifunctional isocyanate compound of the present invention is reacted with the at least one bioactive agent of the present invention in a solution with water.

The Examiner also rejected Claims 1,3-4,7-12,15-16,19,25 and 69 “on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 7,264,823 B2, for the reasons set forth in the previous office action filed 1113012007”. Specifically, the Examiner asserted that:

Applicant's arguments filed 04/30/2008 have been fully considered but they are not persuasive.

Applicants assert that for the reasons set forth above for the 102(e) rejection over Beckman the reference does not disclose or teach the claimed invention.

For the reasons noted above by the examiner Beckman is still an obviousness type double patenting rejection because as stated above applicant's attempted limitation that the isocyanate compound and bioactive agent are reacted in a solution with water is a product by process type of limitation. Since the claims are drawn to a composition the method to make the polyurethane does not alleviate the double patenting rejection over Beckman.

Applicants respectfully traverse the Examiner's rejection. For the reasons set forth above, Beckman et al. does not disclose or suggest the present invention.

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In view of the above amendments and remarks, Applicants respectfully requests that the Examiner, indicate the allowability of the Claims, and arrange for an official Notice of Allowance to be issued in due course.

Respectfully submitted,
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